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Review Article

Prediabetes; Prevention and Management: A Review Article

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ABSTRACT

Pre-diabetes is the state of hyperglycemia at an intermediate stage in which parameters of blood glucose are above standard value but less than the threshold of diabetes. Diabetes mellitus is measured as a risk factor with a high probability of its development. Although the analytic measures for pre-diabetes are not the same in different international professional organizations, the danger of diabetes development is still in height, with conversion rates ranging from 5% to 10% per year. Databased studies propose a relationship between diabetic complications and pre-diabetes like early kidney disease, early retinopathy, small fiber neuropathy and the danger of macrovascular disease. Numerous analyses have revealed the effectiveness of daily routine interpositions in preventing diabetes, with a comparative danger decrease of 40% to 70% in prediabetic adults. Though there is cumulative indication that drug therapy is effective in preventing diabetes in prediabetic adults, drug options for treatment rather than metformin are related with side effects that bound their usage in prediabetics. There are no studies of systematic assessment of the healthiness consequences associated with prediabetes among Children. The effect of pharmacology treatment of pre-diabetes on development and growth in children during adolescence is unidentified. Secondary involvement with metformin pharmacology treatment is recommended for speculative persons, but the standards for assessing the advantage of such primary interference, the longstanding cost-effectiveness of such treatment is still uncertain. Pharmacological treatment should be cast-off with care in prediabetic children. Although pre-diabetes is usually asymptomatic, pre-diabetes always occurs before diabetes develops. The high blood sugar level persists and therefore pre-diabetes cannot be considered completely mild. Conclusions: The purpose of this review is to define the difficulties related with the analysis of pre-diabetes, the potential adverse outcomes of pre-diabetes, and the treatment opportunities and validation of its practice in the context of pre-diabetes.

INTRODUCTION

Diagnosis of Prediabetes: Various organizations have defined pre-diabetes using non-uniform criteria. The WHO has demarcated pre-diabetes as a condition of moderate hyperglycaemia by means of 2 precise constraints: Impaired fasting glucose is definite as fasting glucose between 6.1 mmol / L to 6.9 mmol / L or FBS 110-125 mg / dl and impaired glucose tolerance definite as a glucose concentration in plasma of 7.7-11.0 mmol / L (140-200 mg / dL) for 2 hours afterwards taking oral glucose load (75 g or double of it) based on 2 hours OGTT [1-2]. The ADA has the same threshold (140-200 mg / dL) for IGT but a lesser threshold (100-125 mg / dL) for IFG and has HbA1C grounded criteria (5.7% to 6.4%) for the definition of pre-diabetes A1c (HbA1c) [3-4]. Numerous analyses have revealed a weak association between IFG, IGT and HbA1c [5]. The helpfulness of diagnosing diabetes or pre-diabetes with IGT and IFG is questioned because these glycaemic cut-offs do not take into account the pathology associated with diabetes and the likelihood of progressing towards diabetes in the future [6]. These cut-offs point also lose

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their reliability due to reduced sensitivity of these tests in children and adults. While HbA1c is supposed to signify mean blood levels of sugar and ideally must more accurately reflect hyperglycaemia, it is not completely accurate. HbA1c is largely resolute by hereditary influences not dependent on blood sugar values and can be an inaccurate means for measuring normal sugar levels in blood [7]. Though there is reasonable concern about the analytical principles for pre-diabetes, pre-diabetes is less reproducible (about 52%) than diabetes (about 73%). Grounded on the accessible suggestion, it seems that pre-diabetes, definite by several substitute criteria, comprises of a lapping group of people at one or more time blood glucose irregularities[8-9]. It is probable that the existence of IGT and IFG may identify patients with various pathological anomalies in metabolism of glucose, and the incidence of both indicates a further deterioration in general homeostasis of glucose metabolism.

Prediabetes Prevalence: There have been studies of an expanded frequency of mean diabetes and FPG in both industrialized and under developing states [10]. The National Diabetes Statistics Description by the Centers for Disease Control and Prevention proposes that somewhere in the range of 2009 and 2012, 37% of American grown-ups beyond 20 years old and 51% of those beyond 65 years old had prediabetes, as estimated by glucose levels on void stomach or HbA1c [11]. Worldwide IGT frequency was assessed at 343 million (7.8%) in 2010, arriving at 5.8% in Southeast Asia and 11.4% in the nations of the North America and the Caribbean area. The IDF assesses that by 2035, the pervasiveness of pre-diabetes overall will increment to 471 million[12].

Health Risks Associated With Prediabetes Progression to diabetes: The proportion of transition from pre-diabetes to diabetes varies depending on the features of the people and the standards applied to define pre-diabetes. In meta-analysis held in 2007 about the prediabetes progression to diabetes, the yearly prevalence was 6-9% for isolated IGF, 4-6% for lonely IGT and 15% for isolated IGF and IGT[13-14]. The studies available earlier to 2004 were included in this meta-analysis. The yearly frequency of transition from pre-diabetes to DM were comparable in the large studies described below. In the Study of Diabetes Prevention Program, the diabetes incidence in the control group was 11%[15]. In the USA, International Atherosclerosis analysis, the yearly prevalence of DM in the group of IFG was just over 4.2%. In Health Management Center study of Toranomon Hospital, the frequency of DM was 7.7% to 6.4% in the HbA1c group and 8.9% in the group of IFG. The collective 20-year diabetes mellitus incidence in people with IGT definite by relapse of OGTT in the control group was over 90% testified by the China Da Qing Diabetes Prevention Study (CDQDPS)[16]. It has been shown that the usage of ADA criteria versus criteria of WHO to describe pre-diabetes correspondingly affects the diabetes mellitus incidence, with less morbidity in those definite by criteria of ADA in comparison to the WHO diabetes criteria. A diabetes risk assessment grounded on a more available factors such as gender, age, fasting glucose, ethnicity, HDL cholesterol, systolic blood pressure, diabetes history and BMI has been shown to be better predictive of diabetes[17-18].

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Variable	Studies	Sample size	Positive cases	Prevalence, % (95% CI)	I2	95%, Prediction interval	p-Heterogeneity	p Egger	P-Difference
Prediabetes	9	88702	6443	11.62 (7.17–16.97)	0.998	(0.29–35.23)	< 0.001	0.1209	0.8978
Male prediabetes	7	39241	2796	10.98 (6.95–15.79)	0.994	(0.58–31.47)	< 0.001		
Female prediabetes	8	49201	3565	11.40 (6.55–17.40)	0.997	(0.01–37.55)	< 0.001		
Diabetes	15	103063	15429	14.39 (12.51–16.38)	0.984	(7.37–23.23)	< 0.001	0.7296	
Undiagnosed	8	91526	6798	8.60 (6.48–10.99)	0.992	(2.25–18.48)	< 0.001	0.2363	
By Gender								0.7555	0.6063
Male	12	45580	6697	13.80 (11.94–15.77)	0.961	(7.53–21.56)	< 0.001		
Female	13	55678	7992	14.54 (12.50–16.70)	0.973	(7.49–23.40)	< 0.001		
By Setting								0.8733	0.0594
Rural	11	37307	5060	12.72 (10.63–14.97)	0.966	(5.84–21.73)	< 0.001		
Urban	7	61561	9285	15.89 (13.59–18.34)	0.984	(8.23–25.48)	< 0.001		
By Age								0.3720	0.0001
20 to 29	5	2078	110	3.16 (3.62–6.94)	0.493	(1.35–11.05)	0.0915		
30 to 45	4	5935	815	13.71 (12.85–14.60)	0.000	(11.84–15.69)	< 0.001		
46 to 59	4	11165	2517	25.66 (20.60–31.07)	0.966	(5.70–53.57)	< 0.001		
60+	6	10191	3489	33.45 (28.45–38.64)	0.955	(17.14–52.08)	< 0.001		
Time period								0.7296	0.0210
1995–2010	5	42949	5250	11.82 (9.44–14.43)	0.951	(4.56–21.81)	< 0.001		
2011–2020	10	64615	11003	15.77 (13.75–17.89)	0.974	(8.98–24.00)	< 0.001		
Ethnicity								0.1269	<0.0001
Malay	10	56435	7718	15.25 (11.59–19.29)	0.993	(3.70–32.67)	0.0001		
Chinese	9	18057	1949	12.87 (9.73–16.37)	0.974	(3.29–27.38)	0.0233		
Indian	9	7909	1724	25.10 (20.19–30.35)	0.959	(9.14–45.65)	0.0001		
Bumiputeras	9	9699	704	8.62 (5.41–12.47)	0.968	(0.37–25.27)	0.3535		
Others	6	1710	122	6.91(5.71–8.19)	0.000	(5.25–8.76)	0.8290		

Table 1: Summary of overall and subgroup meta-analyses.

The kidney disease and Nephropathy

Various researches have publicized an increased risk of CKD and an association between early kidney disease and pre-diabetes [19]. The contributory nature of this association is still indistinct as it is because of the higher prevalence of DM in this group or to additional aspects related to both hyperglycaemia and renal disease, relative to the effect of pre-diabetes [20]. **Neuropathies:** Pre-diabetes has been found to be associated with autonomic cardiac dysfunction, as manifested by decreased heart rate variability, reduced heart modulation by parasympathetic system, and an augmented incidence of erectile dysfunction in pre-diabetic men. Non-invasive assessment of nerve dysfunction in people with IGT showed suggestively more anomalies, more frequent hyperalgesia and hypoesthesia, and higher heat sensing thresholds perceived by 4 out of 5 cardiovascular response assessments[21-22]. In addition, there is growing evidence suggesting high prevalence of painful sensory neuropathy, idiopathic polyneuropathy, and small fiber neuropathy in pre-diabetic people with Impaired glucose tolerance test. These results recommend that pre-diabetes involves small nerve fibers in unmyelinated formthat transmit temperature, pain and control autonomic functions preceding to the progression of DM[23].

Retinopathy: The DPP study found that approximately 8 percent of participants with pre-diabetes had diabetic retinopathy. Although it is related with an amplified jeopardy of diabetic retinopathy in few researches, these results vary with screening method[24].

Macrovascular disease: Pre-diabetes is related with an amplified danger of evolving macrovascular disease, although it is uncertain that this increased risk is because of the progression to diabetes or prediabetes alone [25]. Although cross-sectional researches have publicised a higher incidence of CAD in people who are pre-diabetic, this association can be confused with the communal causing influences between pre-diabetes and cardiovascular disease.

TREATMENT OPTIONS FOR PREDIABETES

Lifestyle Interventions: The overarching refrain of lifestyle interference plans is changing adjustable risk factors for pre-diabetes and DM by focusing on obesity through increased dietary changes and exercise. The 2 major studies on prevention of diabetes, Finnish diabetes prevention study (DPS) and US DPP study, found valuable impacts of daily routine interferences. In the study of DPP, later to 3 years of follow-up, severe lifestyle modification led to reduce risk about 58%. ILS included changes in exercise and diet to help to lose weight [26]. The loss of

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weight was institute to be the sturdiest forecaster of risk reduction. The study found that for each one-kg loss of weight, the jeopardy of progressing DM in the future is condensed by sixteen percent[27]. The DPS found that the aids depended on the achievement by the participant achieving the intended goals of the involvement. These aims were weight loss > 5%, consumption of saturated fat < 10% of energy intake, <30% total fat intake of energy intake, consumption of 15 g or more of fiber per 1000 kcal [28]. Although these two studies were conducted primarily among Caucasians, similar benefits were found in the Asian population studies.

Pharmacotherapy: In the context of pre-diabetes, various antidiabetic drugs groups such as thiazolidinediones, biguanides, GLP-1 analogues, α-glucosidase inhibitors and non-diabetic therapies and drugs such as bariatric surgery and anti-obesity drugs have been considered. For eras, diabetes continued to be treated with Metformin and supposed to show to produce supplementary positive results like better cholesterol profile and lower body mass index (BMI) [29]. The communal suggestion from inter-individual studies with IGT showed a 45% decrease in the jeopardy of progression of type-II diabetes mellitus. Metformin was supposed to be much valuable for those with advanced FPG and BMI. Several scientists have also analysed metformin in children who are obese. The combined data suggested a minimum advantage in terms of reduction in BMI compared to routine life modifications, but the advantage was statistically important and the greatest benefit was only short-term with no difference at 6 and 12 months. Glitazones are synthetic ligands for the peroxisome proliferator-activated γ receptor [30]. They upsurge uptake of glucose and reduce hepatic gluconeogenesis and consumption in peripheral organs, thus decreasing resistance of insulin. In a placebo-controlled and double-blinded diabetes reducing trial with rosiglitazone and ramipril, former was operative in reducing the danger of developing DM by sixty percent after three years, but was related with substantial adverse events with raised frequency of HF (0.6% vs 0.2%) and general cardiovascular issues (2.8% vs 2.2%) in the interventional group in comparison to the group of control [31]. The ACT NOW study showed that pioglitazone reduced the diabetes risk by> 70% in IGT and obese patients. Some of the additional profits were lower diastolic blood pressure, a lower intimal-to-middle carotid thickness ratio, and a higher rise in HDL cholesterol, but these were related with greater gain in weight (about three kg extra than placebo) and edema (13% vs 6% in the control group). In the 3-year prospective, placebo-controlled and double-blinded study of IDPP-2, no variance in the diabetes mellitus incidence between placebo and those who received lifestyle intervention and pioglitazone [32]. In a recent Canadian normoglycemic study, a low-dose grouping of metformin and rosiglitazone was verified contrary to placebo to inspect that this combination therapy of low-dose could reduce the type 2 diabetes mellitus incidence with fewer side effect or not. Significantly fewer cases of diabetes occurred in the active therapy group (15%) in comparison to the group of placebos (40%)[33]. The comparative reduction of risk was 67% and the absolute reduction of risk was 27%; 80% of patients in the group given treatment returned to normoglycaemia in comparison to 54% of patients in the group of control, but there were more reports of diarrhea in patients in the active treatment group (17% vs. 7% in the control group). Generally, there are concerns of safety with thiazolidinediones that limit their use in the treatment of pre-diabetes, including liver toxicity, weight gain, possible link to bladder cancer and increased cardiovascular risk. The Glucosidase inhibitors like voglibose and acarbose protract the total time of carbohydrates digestion and reduce the proportion of absorption of glucose, thus reducing the postprandial increase in glucose. The study of STOP-NIDDM showed that acarbose reduced the diabetes relative risk by 26% over 3.3 years of follow-up in IGT patients. The drug was related with a numeral of GIT side effects counting diarrhea and flatulences. A study in Japan showed a reduction of 40% in the risk of developing DM in risky people with IGT with voglibose in 48-week time. It has same like acarbose side effects, but 7% only patients withdrawn from the drug because of side effects. The anti-obesity drug Orlistat also analysed in the context of pre-diabetes. Orlistat is a lipase inhibitor in gastrointestinal tract cast-off in the management of obesity that works by preventing the dietary absorption of fat about 30%. Studies have shown that after 1.5 years of follow-up, the usage of Orlistat in combination with a low-energy diet is related with high loss of weight (3.8 kg vs 3.9 kg). The XENDOS study also showed a similar finding concerning the effectiveness of Orlistat, with 38% comparative decrease in the risk of developing DM after treatment for four-years [34].

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IDPP (80)	Lifestyle intervention or metformin	3 years	NNT of 6.4 with lifestyle intervention and 6.9 with metformin
DPP (79)	Lifestyle (7% weight loss and 150 minutes of moderate exercise/ week) or metformin	5 years	Reduction in diabetes incidence of 58% with lifestyle modification and 31% with metformin
ACT NOW (82)	Pioglitazone	2.5 years	72% reduction in diabetes incidence
STOP-NIDDM (81)	Acarbose	3.3 years	25% reduction in diabetes incidence
CANOE (84)	Rosiglitazone and metformin	3.9 years	66% relative risk reduction in diabetes incidence and NNT of 4
DREAM (83)	Rosiglitazone	3 years	60% reduction in diabetes incidence
Bariatric surgery (86)	Laparoscopic adjustable gastric banding	4 years	75% reduction in diabetes incidence
Dapagliflozin once-daily and exenatide onceweekly dual therapy: a 24-week randomized, placebo-controlled, phase II study (85)	Dapagliflozin and exenatide	24 weeks	50% reversal to normal glucose tolerance

Table 2: Clinical Trials Showing the Effectiveness of Antidiabetic Drugs to manage Prediabetes

Bariatric surgery: Bariatric surgical procedure involves various methods intended at inducing a restrictive state, malabsorption state, or a mixture of these two to restrict consumption of calories. Commonly used methods comprise laparoscopic gastric banding, Roux-en-Y gastric bypass, duodenal biliary pancreatic resection and sleeve gastrectomy [35]. In an obese Swedish patient, bariatric surgery led to loss of weight (24.2% after two years and 15.9% after ten years) and comparative decline in the risk of DM by 75% in comparison to the control group. Bariatric surgery has also been connected with a reduced incidence of cardiovascular disease, type-II diabetes mellitus, and cardiovascular death in obese adults aged 2 and 10 years [36]. A previous study found that 78% of people with pre-existing diabetes and 98% of people with IGT returned to normal blood sugar levels after gastric bypass surgery.

CONCLUSION

In conclusion, a systematic assessment of the healthiness consequences of pre-diabetes and the reimbursements of early treatment, if any, is needed. Choosing the right results for such a study is crucial. In addition, the standards cast-off to describe pre-diabetes need to be polished based on longstanding medical outcomes. Though these researches may appear necessary, the time required to investigate adverse outcomes in pre-diabetes and the low incidence of these findings may be a restrictive factor for such analysis. There is currently no tangible indication to support clinical strategies for the management of prediabetes. Lifestyle modifications continue to be an important fragment of treating pre-diabetic patients. The usage of pharmacological therapy must be based on distinct approach. When pharmacological therapy is used to manage pre-diabetes, the plan of treatment must be started with aims and endpoints established in advance by the medical doctor. A careful method to the use of pharmacotherapy in children and adolescents is warranted.

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